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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
[illegible]	
ART UNIT	PAPER NUMBER
[illegible]	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/529,722	SQUIRRELL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on *02/07/01*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____.

3.☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1*
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-3 and 5-18 are pending.

The amendment of claims 1, 3, 5, 6, 10 and 14, cancellation of claim 4, and the addition of an abstract in Paper No. 5 is acknowledged.

Claim 18 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants' arguments filed on 02/07/01, paper No. 5, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification/Informalities

1. The abstract of the disclosure is objected to because of the recitation of "said polypeptide product" and "said undesired protein". Legal phraseology should generally be avoided in the abstract. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-3, 6, 10, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. The term "efficiency" in claim 1 is unclear and confusing. The term "efficiency" is not defined by the claim nor the specification and the meaning of this term is unclear. It is suggested that the language "efficiency" be deleted.

4. Claim 1 is rejected because of the recitation of the term "which is a protein whose activity is essential" because it is unclear whether the protein is referring to the polypeptide product or the undesired protein. It is suggested that the term "protein whose activity is essential" be replaced with, for example, "wherein said undesired protein has activity that is essential"

5. As stated in the previous Office action, the term "activity" in claim 1 is a relative term which renders the claim indefinite. Applicants amendment to the claim has not overcome the non-limitations of the term "activity". Applicants will recognize that activity can imply a variety of biological interpretations including enzymatic activity and binding activity. Applicants will also recognize that proteins are known in the art with dual functionality. As these proteins have more than one activity, it would be unclear as to which specific activity Applicants are referring to.

6. As stated in the previous Office action, the term "stable" in claims 1, 10, 15 and 16 is a relative term which renders the claim indefinite. Applicants argue that the level of stability of the polypeptide product is immaterial provided it is more stable than the mutant undesired protein. However, it is unclear from the claim as to the intended degree of stability. For example, stable in terms of maintaining primary amino acid structure or stable in terms of maintaining enzymatic

activity. Without reference to a specific function or activity, the term "stable" in the claims is non-limiting and renders the claim indefinite.

7. The term "unstable" in claims 1, 2, 10, 15, and 16 is a relative term which renders the claim indefinite. See above argument.

8. Claims 5, 7-9, 11-14, and 17 are rejected as being dependent on indefinite claims 1-3, 6, 10, 15 and 16.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 5, 6, 10, and 12-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing and recovering luciferase that is substantially free of a mutant *Escherichia coli* adenylate kinase that is enzymatically inactive at temperatures greater than or equal to 37 ^{o}C using recombinant cells therefore, and methods of producing said cells, does not reasonably provide enablement for a method for producing any polypeptide product that is substantially free of any mutated undesired protein that is unstable under any conditions at which the polypeptide product remains stable using recombinant cells therefore and methods of producing said cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3 (claims 5 and 7-9 dependent thereon), 6 , 10 (claims 11-14 dependent thereon), 15 (claim 17 dependent thereon) and 16 are so broad as to encompass a method of

producing any polypeptide or protein as either a polypeptide product, desired product or recovered product free of an undesired protein, wherein the conditions at which the undesired protein is denatured or unstable and the polypeptide product, desired product or recovered product is stable or intact are any conditions using recombinant cells therefore and methods of producing said cells. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptide products or undesired proteins. In the instant case, the disclosure is limited to a method for production and recovery of luciferase that is substantially free of a mutant *Escherichia coli* adenylate kinase that is enzymatically inactive at temperatures greater than or equal to 37 °C using recombinant cells therefore, and methods of producing said cells.

As stated in the previous office action, the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims without undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). The factors most relevant to this rejection are the scope of the claims, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented. In the instant case, the claims broadly encompass a method of producing any polypeptide product that is substantially free of any undesired protein under any conditions that would denature an undesired protein while maintaining biological activity of the polypeptide product.

Applicants argue that one merely needs to compare the properties of the target protein and the contaminant and identify those mutants that have differential stability under a particular

condition. Applicants further argue that such mutants can be identified by conventional screening techniques or random mutagenesis as described in the specification. However, due to the extreme number of potential target and contaminant proteins as encompassed by the claims along with a variety of potential conditions (temperature, pH, pressure, presence of chemical denaturants, etc.), there remains significant unpredictability of this process with an expectation of obtaining the desired biological result. The Examiner notes that the thermostable luciferase (see for example p 5, lines 29-31) and the thermolabile adenylate kinase (see for example p 5, lines 11-13) were well characterized in the art at the time of the invention. Therefore, Applicants merely needed to apply the method without first identifying mutations that resulted in the desired biological activity, i.e., thermostability of luciferase and thermolability of adenylate kinase. The Examiner also notes that it was known in the art that adenylate kinase is an undesired by-product in the conventional (i.e., chromatographic) purification of luciferase. Therefore, Applicants could easily apply the prior art to isolate and mutate the polynucleotide encoding adenylate kinase. This level of knowledge is unlikely to be the case in the vast majority of cases encompassed by Applicants' claims. The ordinarily skilled artisan seldom has knowledge regarding the primary contaiminant(s) in a purification and, even if the contaminant(s) can be identified, they are likely to be virtually uncharacterized proteins. Isolating a mutant protein for such uncharacterized proteins would clearly require undue experimentation. However, Applicants have failed to provide guidance as how one specifically identifies and isolates <u>any</u> undesired protein that results in contamination of an otherwise purified polypepetide product, and further produces mutants thereof which differ in stability from some other protein without knowledge to the activity of the contaminant or a gene encoding therefore.

Applicants argue further that there is no reason why these methods could not be broadly applied. However, the instant specification provides guidance only for a method for producing luciferase free of enzymatically active adenylate kinase. Furthermore, the specification provides no guidance or suggestion as to other specific proteins and/or specific conditions that may be employed by this method.

Thus, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of producing any polypeptide product that is substantially free of any undesired protein under any conditions that would denature an undesired protein while maintaining biological activity of the polypeptide product. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

10. The previous rejection of claims 1-5 and 7-17 under 35 U.S.C. 103(a) has been withdrawn. Upon reconsideration of the rejection, the Examiner notes that the prior art teaches a method of isolating a thermostable enzyme free of undesired contaminants by heat inactivation of said contaminants in a cell (Backman et al.). However, the prior art does not specifically teach nor suggest a method of isolating a thermostable enzyme free of a contaminant by genetically modifying the contaminant for the purposes of creating a thermolabile mutant and using heat

denaturation to remove the contaminant activity from the thermostable enzyme. Therefore, the claimed methods would be at best obvious-to-try.

11. No claim is in condition for allowance.

Applicant's addition of the abstract and amendment of claims 1 and 10 necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura

Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

February 26, 2001

REBECCA E. PROUTY
PRIMARY EXAMINER
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1600